Commentary

The International Sepsis Forum's controversies in sepsis: my initial vasopressor agent in septic shock is norepinephrine rather than dopamine

Vinay K Sharma[1] and R Phillip Dellinger[2]

[1]Fellow, Critical Care Section, Cooper Health System, Camden, New Jersey, USA
[2]Head, Critical Care Section, Cooper Health System, Camden, New Jersey, USA

Correspondence: R Phillip Dellinger, dellinger-phil@cooperhealth.edu

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Abstract

Vasopressor agents are often used in patients with septic shock when aggressive fluid resuscitation fails to correct hypotension. Dopamine and norepinephrine are two such vasopressor agents. In the past, fear of potential excessive vasoconstriction, with resultant end-organ hypoperfusion, restricted the use of norepinephrine in septic shock, relegating it to a second-line agent. However, recent data suggest that this relegation is unmerited and that norepinephrine may even be superior to dopamine in some respects, and should be considered as the preferred first-line agent. In the present commentary we review the evidence supporting the use of norepinephrine as the agent of choice in the treatment of septic shock.

Keywords dopamine, norepinephrine, septic shock

Norepinephrine and dopamine are the common vasopressor agents used in patients in septic shock who do not respond to fluid resuscitation. Norepinephrine is a potent α_1-adrenergic agonist with a weaker but still significant β-adrenergic agonist effect. It increases blood pressure mainly by increasing systemic vascular resistance as a consequence of its vasoconstrictive effects. Dopamine has agonistic effect on a variety of different receptors, depending on the dose used. At doses below 5 μg/kg per min it acts predominantly on dopamine receptors (mainly the vascular D_1 receptor); at doses between 5 and 10 μg/kg per min its β-adrenergic agonist effects are dominant; whereas at doses above 10 μg/kg per min its α_1-adrenergic agonist action predominates. The American College of Critical Care Medicine and the Society of Critical Care Medicine in 1999 published practice parameters for the hemodynamic management of patients in septic shock [1]; despite 197 listed and ranked references, less than a handful of reports could be categorized as large, prospective, and comparative in determining the best vasopressor with which to raise arterial pressure.

Traditionally, the use of norepinephrine in patients with shock has been restricted by the fear of excessive vasoconstriction that may result in end-organ hypoperfusion. In the past it was usually given only when other vasopressor agents failed, and thus such patients would be predicted to have a poor outcome. Recent studies indicate that the fear of deleterious effect was unwarranted and that norepinephrine may have a role as a first-line vasopressor agent in patients with septic shock. There are a number of reasons to consider using norepinephrine first.

Norepinephrine produces less tachycardia

Norepinephrine-induced increase in blood pressure occurs with little change in the heart rate. This is because the weak β-agonist chronotropic effect of norepinephrine is counterbalanced by an increased venous capacitance

CI = cardiac index; MAP = mean arterial pressure.

constriction effect on the right heart baroreceptors. In a recent study conducted by LeDoux and coworkers [2] involving 10 patients with septic shock, the dose of norepinephrine was titrated up in stages to achieve a mean arterial pressure (MAP) of 65 mmHg, 75 mmHg, and finally 85 mmHg. The mean doses of norepinephrine required to maintain these MAPs were 23, 31 and 47 μg/min, respectively, whereas the mean heart rates at these doses were 97, 101 and 105 beats/min, respectively. In contrast, tachycardia is among the major undesirable effects of dopamine at doses exceeding 5 μg/kg per min. In a crossover study that compared dopamine and norepinephrine [3], heart rate was found to be significantly higher while patients were on dopamine. The heart rate decreased from a mean of 100 beats/min to 91 beats/min in nine patients when dopamine was changed to norepinephrine, and increased from a mean of 92 beats/min to 134 beats/min in 10 patients when norepinephrine was changed to dopamine.

Increased cardiac index

In years past norepinephrine was linked by many to digital ischemia and decreased cardiac index (CI). Although this is true if it is used in hypovolemic shock and may occur with cardiogenic shock, that is not the case with septic shock. In fact, norepinephrine has been shown to produce some increase in CI. In the study conducted by LeDoux and coworkers [2], the increasing doses of epinephrine required for the three levels of MAP mentioned above resulted in progressive increase in the CI (mean values 4.7, 5.3, and 5.5 l/min per m^2, respectively). Dopamine also increases CI, primarily due to an increase in stroke volume, but also partly due to an increase in heart rate.

No deleterious effect on cerebral perfusion pressure

Catecholamines normally have no effect on cerebral blood flow, which is at least partly due to their inability to cross the blood–brain barrier. After severe brain injury, however, the blood–brain barrier may be locally disrupted and the autoregulation of cerebral blood flow impaired. In this situation it is possible that the cerebral vascular response to catecholamines may be altered. The cerebral effects of dopamine and norepinephrine were compared in a recent crossover study conducted in 19 patients with severe head trauma requiring vasopressor therapy [3]. The cerebral perfusion pressure was found to be significantly lower for the same MAP while the patients were on dopamine. The cerebral perfusion pressure increased from a mean of 66 to 69 mmHg when dopamine was changed to norepinephrine, and decreased from a mean of 70 to 61 mmHg when norepinephrine was changed to dopamine.

No effect on the hypothalamic–pituitary axis

Dopamine has long been known to suppress prolactin, thyroid-stimulating hormone, and luteinizing hormone secretions in healthy persons. D_2 receptors have been identified in the anterior pituitary and in the hypothalamic median eminence. The effect of dopamine on anterior pituitary function in critically ill patients was reviewed by Van den Berghe and de Zheger [4]. Dopamine has been found to suppress the circulating concentrations of all anterior pituitary hormones except for cortisol. These investigators noted that a similar pattern is seen in some patients during prolonged critical illness and suggested that endogenous dopamine may play a role in the endocrine response to critical illness. They concluded that the major effect of prolonged dopamine infusion on the endocrine system is unlikely to be beneficial and may even be harmful to the metabolic and immunologic homeostasis of the severely ill patient. Norepinephrine does not have any known deleterious effects on the hypothalamic–pituitary axis.

More effective and better outcome as compared with dopamine

There are few comparisons between the different vasopressor agents. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. In open-label trials, norepinephrine was shown to increase MAP in patients who remained hypotensive after fluid resuscitation and dopamine administration. In a randomized, double-blind trial, Martin and coworkers [5] compared norepinephrine with dopamine in 32 patients with septic shock. Target MAP and CI was achieved with dopamine in 31% of patients, whereas the same targets were achieved in 93% of patients with norepinephrine ($P < 0.001$). Of 11 patients who did not respond to dopamine and remained hypotensive and oliguric, 10 were successfully treated with the addition of norepinephrine. In a more recent prospective, nonrandomized study by the same investigators [6], norepinephrine was compared with dopamine in 97 patients with septic shock. Mortality was lower in patients on norepinephrine at day 7 (28% versus 40%; $P < 0.005$), day 28 (55% versus 82%; $P < 0.001$), and hospital discharge (62% versus 84%; $P < 0.001$). Using stepwise logistic regression analysis, norepinephrine was found to be the only factor associated with significantly improved survival ($P = 0.03$). Despite the drawback of lack of randomization, this is the first study, to our knowledge, to link a survival advantage with any vasopressor.

Amelioration of splanchnic hypoperfusion

Studies evaluating the effects of catecholamines on splanchnic blood flow have produced conflicting results. In a study conducted by Ruokonen and coworkers involving patients with septic shock [7], the effect of norepinephrine on splanchnic blood flow was considered unpredictable, whereas dopamine caused a consistent and statistically significant increase in splanchnic blood flow. However, Maynard and colleagues [8] were unable to show any effect of dopamine on intramucosal pH, whereas Neviere and colleagues [9] found that gastric mucosal blood flow was

decreased and intramucosal pH was unchanged with dopamine. Meier-Hellman and coworkers [10] concluded that, provided cardiac output is maintained, treatment with norepinephrine alone is without negative effects on splanchnic tissue oxygenation. One study [11] demonstrated that norepinephrine preserves splanchnic blood flow better than does dopamine. In that study, 20 patients with septic shock were randomly assigned to norepinephrine or dopamine titrated to maintain an MAP above 75 mmHg. The gastric intramucosal pH increased significantly in patients on norepinephrine but decreased significantly in those receiving dopamine ($P < 0.001$).

Increased glomerular filtration pressure

In patients with hypovolemic shock, norepinephrine can have severe detrimental effects on renal perfusion. However, in hyperdynamic septic shock, urine flow is believed to decrease mainly as a result of lowered renal perfusion pressure. Norepinephrine has a greater effect on efferent than on afferent arteriolar resistance, and thus increases renal perfusion pressure. In fact, studies have shown that the addition of norepinephrine to patients with septic shock can significantly increase urine output [12,13].

Decreased serum lactate concentration

Increased blood lactate concentration may reflect anaerobic metabolism because of hypoperfusion, but it is also a strong prognostic indicator. In the study conducted by Martin and coworkers [5], initial lactate levels were found to be elevated and patients receiving norepinephrine showed a statistically and clinically significant decrease in levels. In another study [14] treatment with a combination of norepinephrine and dobutamine resulted in a significant decrease in lactate levels.

Conclusion

In summary, although there is no high level evidence that choosing norepinephrine as the vasopressor of choice in septic shock leads to a better outcome, there is considerable physiologic support for that choice. Prospective randomized trials would be needed to establish this.

Competing interests

None declared.

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